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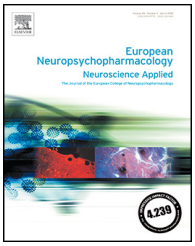

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Characterizing the nature of emotional-associative learning deficits in panic disorder: An fMRI study on fear conditioning, extinction training and recall

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Abstract
Emotional-associative learning represents a translational model for the development, maintenance and treatment of anxiety disorders such as panic disorder (PD). The exact nature of the underlying fear learning and extinction deficits however, remains under debate. Using a three-day paradigm to separate the distinct learning and consolidation processes, we aimed to gain insights into the neurofunctional substrates of altered fear conditioning, extinction training and recall in PD. In contrast to studies employing one-session fear conditioning paradigms, a differential fear conditioning and delayed extinction task was conducted for the purpose of disentangling neural networks involved in fear acquisition, extinction training and recall of extinction memories. Using functional magnetic resonance imaging (fMRI), quality-controlled datasets from 10 patients with PD and 10 healthy controls were available from three consecu-

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tive days (day 1: acquisition; day 2: extinction training; day 3: extinction recall) with neutral faces serving as CSs and an aversive auditory stimulus (panic scream) as US.
PD patients showed heightened fear circuitry (e.g. right amygdala and left insula) activation during early acquisition and prolonged activation in the right insula, left inferior frontal operculum and left inferior frontal gyrus during extinction recall compared to healthy controls.
Stronger neural activation in structures conferring defensive reactivity during early acquisition and extinction recall may indicate the accelerated acquisition of conditioned responses, while extinction recall may be attenuated as a function of PD pathophysiology. Future studies should investigate the predictive value of experimental measures of extinction recall for clinical relapse.

1. Introduction

Emotional-associative learning serves as a translational model for the development, maintenance and treatment of anxiety disorders (Mineka and Oehlberg, 2008) as it represents a key paradigm for understanding the neurobiology of fear and the mechanisms underlying variations in fear memory strength (Johnson et al., 2012). Extinction training, the laboratory analogue to behavioral exposure (Bouton et al., 2001) is currently conceptualized as forming a new memory trace which confers the inhibition of the formerly learned fear reaction when the extinction memory is recalled (Milad and Quirk, 2002). Although extinction has been extensively studied in animals, less is known about alterations in extinction training and recall in anxiety disorders. Of note, most studies used one-session fear conditioning and extinction protocols neither allowing for memory consolidation nor for assessing extinction recall – a phenomenon with high translational value for better understanding the problem of clinical relapse.

Fear conditioning enables the organism to avoid future threats in that important information (conditioned stimuli, CS) signaling a potential threat (unconditioned stimulus, US) elicits defensive reactions (conditioned fear response, CR). During fear extinction training, a second fear-inhibitory learning process is initiated, resulting - after successful consolidation - in two memory traces existing in parallel: the conditioning memory (CS-US) and the extinction memory (CS-no-US). When encountering the CS after extinction training, both memory traces can be activated, with the magnitude of fear reactions being dependent on the extent to which the extinction memory is activated (Milad et al., 2006). The neurophysiology of fear acquisition is well identified (Maren and Quirk, 2004) and highlights the role of the amygdala as central structure for the acquisition and expression of learned fear in rodents (Duvarci and Pare, 2014; LeDoux, 2000) and humans (Phelps et al., 2004; Sehlmeyer et al., 2009). Animal and human neuroimaging studies have also shown overlapping neural systems involved in extinction learning, corroborating the role of the amygdala and the infralimbic cortex (IL) in rodents or, respectively, the ventromedial prefrontal cortex (vmPFC) as its human homologue (Delgado et al., 2008; Milad et al., 2014). In comparison to the acquisition, amygdala activity decreases as extinction proceeds while activity in the IL/vmPFC relatively increases (Milad et al., 2007) throughout extinction learning as the IL/vmPFC projects to inhibitory neurons within the amygdala (Milad and Quirk, 2012). The IL/vmPFC also constitutes a key region for extinction recall (Davis, 1992; Milad and Quirk, 2002) just as the hippocampus, indicating the importance of contextual information for retaining extinction memory (Kalisch et al., 2006; Milad et al., 2007).

Fear conditioning seems to play a pivotal role for the development and maintenance of PD, although the exact nature of the underlying fear learning and extinction deficits remains under debate (Duits et al., 2015; Lueken et al., 2014). Gorman et al. (2000, 1989) presented a neuroanatomical hypothesis according to which the behavioral symptoms of PD are mediated via a neural network encompassing the amygdala, thalamus, hypothalamus, hippocampus, periaqueductal grey (PAG) and locus coeruleus. Accordingly, PD patients are thought to have an abnormally sensitive fear network with lowered activation thresholds resulting in excessive activation. Threat cues can then trigger defensive behavior by activating survival circuits in the brain, probably mediated by the PAG (Hamm et al., 2014). To date, several neuroimaging studies have corroborated the pivotal role of certain neural networks for PD pathophysiology (Dresler et al., 2013; Graeff and Del-Ben, 2008; Lueken et al., 2014; Sobanski and Wagner, 2017). Recent functional studies suggest aberrant activation in an extended network comprising the brainstem, insula, anterior and midcingulate cortices as well as medial and lateral parts of the PFC in PD (Sobanski and Wagner, 2017). Additional pathophysiological models of PD encompass among others interoceptive conditioning processes (e.g., Benke et al., 2018; Bouton et al., 2001; Khalsa and Lapidus, 2016; Pappens et al., 2015) or suffocation false alarm theory (Klein, 1993) resulting in CO_2 hypersensitivity (Esquivel et al., 2010; Leibold et al., 2016), pointing towards the relevance of brain systems beyond fear conditioning circuits such as the periaqueductal grey and brainstem (Goossens et al., 2014; Wemmie, 2011). Regarding fear conditioning and extinction, altered neural processing of safety cues (Kircher et al., 2013; Tuescher et al., 2011), a proclivity towards fear overgeneralization (Lissek et al., 2009) or resistance to extinction indicated by a prolonged retention of the CR (Michael et al., 2007) have been considered to be accountable for deviant fear learning processes in PD.

Previous research on fear conditioning and extinction as a pathophysiological marker of PD is however limited by two major shortcomings: First, fear acquisition and extinction are usually conducted within one session (Milad et al., 2007)

thus not allowing the fear and extinction memory to consolidate. Consequently, alterations pertaining to extinction training of one-session paradigms cannot be unequivocally interpreted as truly representing fear inhibitory learning, but rather a mixture resulting from the recall of the fear memory and the extinction process. Second, the recall of extinction memories is rarely tested at all (as compared to animal studies that typically include testing on a separate day). Therefore, knowledge about deficits in extinction recall as a correlate of PD is virtually not available, limiting the translation of animal findings to the patient level. From a clinical perspective, it is however essential to test whether patients recall their extinction memories, i.e. actively inhibit fear reactions, when encountering the CS again. The phenomenon of relapse after successful behavioral exposure frequently seen in anxiety disorders (Taylor et al., 2012) could thus be interpreted as a failure to consolidate or recall extinction memories.

Following this translational perspective, the present study aimed to closer match fear conditioning and extinction protocols based on animal research to the clinical level. Investigating the neural substrates of fear conditioning, extinction training and recall separated by distinct overnight consolidation phases, we applied a three-day fear conditioning and delayed extinction paradigm. Regarding the acquisition of newly conditioned fears during day 1, we expected patients to show heightened activity in defensive networks encompassing the amygdala and insula as an indicator of exaggerated conditionability (e.g., Mineka and Oehlberg, 2008; Phelps et al., 2004). Second, when recalling the fear conditioning memories at the beginning of day 2, we expected patients to show stronger activation of these networks compared to controls. After completion of the extinction training and following overnight consolidation, we hypothesized patients will show impaired recall of the extinction memory on day 3 as represented by stronger and prolonged activation of defensive networks compared to controls, where fear inhibition should take place faster.

2. Experimental procedures

2.1. Participants

As part of the multicenter national research network "Panic-Net" (2nd funding period) a total of $n = 20$ quality-controlled datasets with full data from all three days were included in this analysis, consisting of $n = 10$ patients with PD and $n = 10$ healthy controls (HC). Patients were recruited from the psychotherapy outpatient center at Technische Universität Dresden; HC responded to local advertisements. Patients and controls were matched for age, gender, smoking status, handedness (only right-handers) and educational level.

Patient inclusion criteria comprised a primary diagnosis of PD according to DSM-IV-TR criteria (American Psychiatric Association, 2000), age between 18–65 years and a score ≥ 4 at the Clinical Global Impressions Scale (CGI; Guy, 1976). Patients completed the Panic and Agoraphobia Scale (PAS; Bandelow, 1999), Anxiety Sensitivity Index (ASI; Reiss et al., 1986) and the Beck Depression Inventory (BDI; Beck et al., 1961). Overall anxiety severity was rated by trained clinicians using the Structured Interview Guide for the Hamilton Anxiety Scale (SIGH-A; Shear et al., 2001). Exclusion criteria encompassed suicidal intent, psychotic and bipolar disorders, borderline personality disorder, substance dependency, ongoing treatment, antidepressant or anxiolytic pharmacotherapy, or any medical disease that could account for patientsśymptoms. All other comorbidities including unipolar depression and further anxiety disorders were allowed as long as they were not of primary clinical concern. HC were free of past or current psychiatric, neurological or medical illness. Pregnancy and MRI-related contraindications were general exclusion criteria for both groups. Sample characteristics were analyzed using χ^2 and t-tests as implemented in SPSS 24 (IBM Corp., Armonk, NY, 2016) with $p < 0.05$ serving as a statistical threshold. After receiving a detailed description of the study, participants provided informed written consent. The study was approved by the ethics committee of the Technische Universität Dresden (EK 62,022,010).

2.2. Fear conditioning and delayed fear extinction paradigm

A differential fear conditioning and delayed extinction paradigm was conducted on three consecutive days (habituation & fear acquisition on day 1; extinction training on day 2; extinction recall on day 3; see Fig. 1 for details). In addition to the fear conditioning procedure on day 1, participants completed a semantic priming task (Yang et al., 2016) and an agoraphobia symptom provocation task ("Westphal paradigm", Wittmann et al., 2011). Two neutral pictures of male faces (Ekman faces, Ekman, 1992) served as CSs with a reinforcement rate of 100%, while an aversive panic scream (2 s, 95 dB, calibrated with an artificial ear) served as auditory US. Assignment of the faces as CS+ or CS− was counterbalanced and stimuli were presented in a pseudorandomized order (max. of two repetitions of each stimulus). A jittered inter-stimulus-interval between 7.7–16.2 s was used after each trial to allow for the assessment of skin conductance responses (SCRs) within a time window of 1–5 s after stimulus offset. Every experimental phase (see Fig. 1) consisted of 8 presentations of each CS (and, during acquisition, the US, respectively). The entire paradigm consisted of nine experimental phases allowing for sufficient time resolution for the respective learning and recall phases (day 1: habituation (H), early and late acquisition (A1, A2); day 2: recall CR (ET1), early and late extinction training (ET2, ET3); day 3: return of fear (ER1), early and late extinction recall (ER2, ER3); duration at each day approx. 15 min). Online-recordings of stimulus-specific SCRs and subjective valence and arousal ratings were collected as indicators of successful conditioning and contingency knowledge. Ratings were assessed after each phase using a nine-point Likert scale for both CSs (for valence: 1, 'very positive' to 9 'very negative' ; for arousal: 1, 'very low' to 9 'very high'), presented in counterbalanced order. Stimuli were presented via MR-compatible LCD goggles and headphones using Presentation 14 (Neurobehavioral Systems; www.neurobs.de). Awareness of the CS-US contingency was assessed in a postexperimental interview (see supplemental data for details).

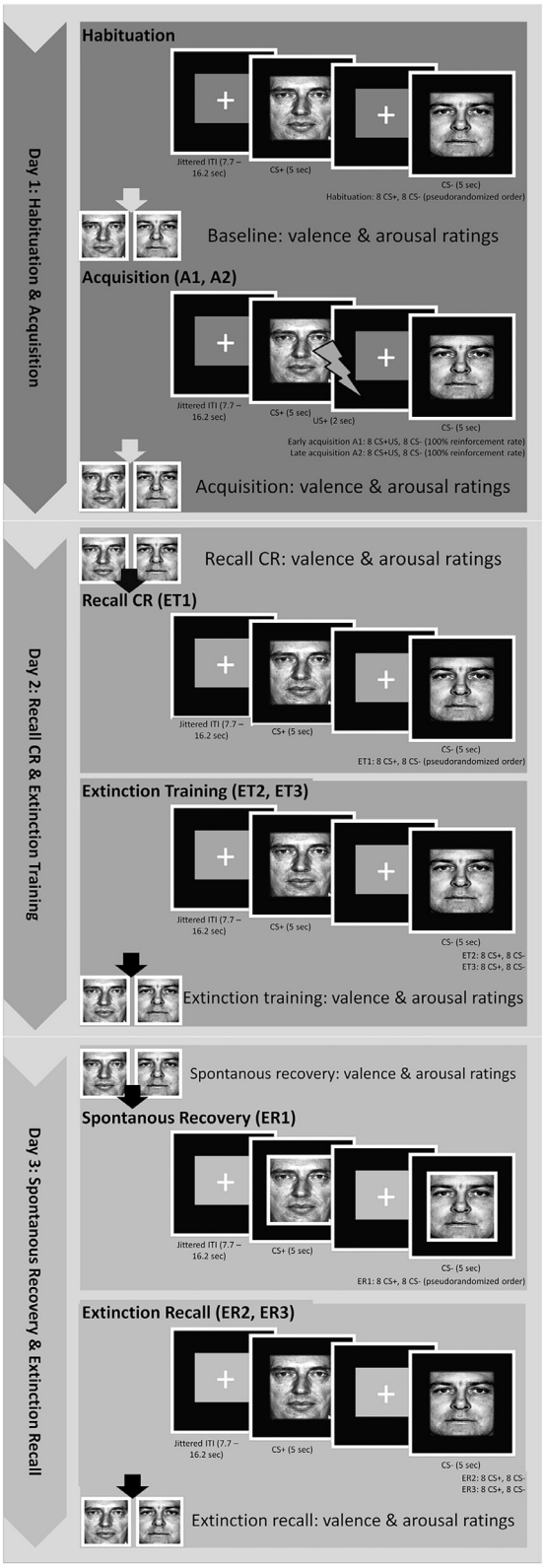

Fig. 1 Differential fear conditioning and delayed extinction task. Day 1: habituation & acquisition (A1, A2); day 2: recall conditioned response (CR) after overnight consolidation (ET1) and extinction training (ET2, ET3); day 3: return of fear (ER1) and extinction recall after overnight consolidation (ER2, ER3). CS+: conditioned stimulus (CS) paired with the US. CS−: CS never paired with the US. US: unconditioned stimulus (human panic scream).

2.3. fMRI data acquisition and analysis

MRI images were acquired on a 3-Tesla Trio-Tim MRI whole-body scanner (Siemens, Erlangen, Germany). On day 1, 368 and on day 2 and 3 356 axial functional images [echo-planar imaging (EPI): matrix 64×64, 41 slices interleaved (bottom-up), field of view (FOV) = 192, voxel size = $3 \times 3 \times 3$ mm, echo time (TE) = 25 ms, repetition time (TR) = 2.5 s] covering the whole brain were acquired using a tilted angle of 20° to the anterior - posterior commissure (AC-PC) to reduce susceptibility artefacts in inferior brain areas (Deichmann et al., 2003). In addition, a structural data set [magnetization prepared rapid gradient echo (MPRAGE): matrix = 256×256, slices = 176, FOV = 256, voxel size = $1 \times 1 \times 1$ mm, TE = 2.26 ms, TR = 1.9 s, flip angle = 9°] was recorded. The 5 initial scans were discarded to avoid T1 saturation effects. Data analyses were carried out using Statistical Parametric Mapping (SPM8; www.fil.ion.ucl.ac.uk) implemented in MATLAB®R2012a (Mathworks Inc., USA.), applying a high-pass filter (cutoff period, 128 seconds) to remove low-frequency fluctuations in the blood-oxygen-level-dependent (BOLD) signal. Functional images were preprocessed, encompassing slice time correction to correct for differences in image acquisition time between slices, realigned and unwarped to correct for movement artefacts. We coregistered T1 and EPI images, segmented the coregistered T1 images and normalized EPI images ($3 \times 3 \times 3$ mm resolution) using T1 segmentation maps into standard stereotactic space (Montreal Neurologic Institute template; $3 \times 3 \times 3$ mm). Normalized EPI data were smoothed with a Gaussian kernel of 6 mm FWHM (full-width at half-maximum). First-level statistical analysis was done for all subjects applying the general linear model (GLM). Using an event-related design, realignment parameters and rating phases were included as regressors of no interest. The BOLD response was modelled for each event type (CS+, CS−, US) and phase, including each day as a separate session (day 1: H, A1, A2; day 2: ET1, ET2, ET3; day 3: ER1; ER2; ER3) convolved with the canonical hemodynamic response function within the framework of the GLM, resulting in eight regressors of interest on day 1 (HCS+, HCS−, A1CS+, A1CS− A1US, A2CS+, A2CS−, A2US), and six regressors of interest on day 2 and 3 (day 2: ET1CS+, ET1CS−, ET2CS+, ET2CS−, ET3CS+, ET3CS−; day 3: ER1CS+, ER1CS−, ER2CS+, ER2CS−, ER3CS+, ER3CS−). Parameter estimates (beta values) and *t*-statistic images were calculated for each subject. The group analysis was performed by including contrast images into a full factorial analysis. As patients and controls were well matched, no additional covariates were included. T-contrasts of interest were computed separately for each full phase (e.g. acquisition) and its subphases (e.g. A1, A2). In a first step we investigated the main task effects on differential conditioning (CS+ > CS−) in the entire group (A: CS+ > CS−; A1: CS+ > CS−; A2: CS+ > CS−; ET: CS+ > CS−; ET1: CS+ > CS−; ET2: CS+ > CS−; ET3: CS+ > CS−; ER: CS+ > CS−; ER1: CS+ > CS−; ER2: CS+ > CS−; ER3: CS+ > CS−). In a second step, we tested for group differences (PD > HC; HC > PD) in these respective contrasts. As we used this novel paradigm for the first time, exploratory whole brain results are reported to allow for better comparability with future studies on delayed extinction training

and recall. Due to the small sample size and limited statistical power, a liberal significance threshold of $p < 0.005$ uncorrected with a cluster size of $K_E = 15$ voxels was conducted, using the automated anatomical labelling atlas (AAL; Tzourio-Mazoyer et al., 2002) for cluster identification. Beta values from significantly activated brain clusters were extracted using a 5 mm sphere and used for bar graph visualization.

2.4. Subjective ratings and SCR data acquisition and analysis

Subjective ratings as indicators of contingency knowledge were recorded after H (used as baseline values), A2 (indicating differential fear conditioning), prior to ET1 (ET-pre; indicating recall of CR after consolidation), following ET3 (ET-post; indicating extinction training effects), prior to ER1 (ER-pre; indicating return of fear) and after completion of ER3 (ER-post; indicating extinction recall). A three-factorial repeated Analysis of Variance (ANOVA) as implemented in SPSS 24 (IBM Corp., Armonk, NY, 2016) with the two within-subject factors "phase" (H, A, ET1, ET3, ER1, ER3), "CS" (CS+, CS−), and the between-subject factor "group" (PD, HC) was used to test for main and interaction effects, followed by pairwise comparisons to localize the direction of effects.

SCRs were recorded during scanning with Ag/AgCl electrodes (MES Medizintechnik, Munich, Germany) attached to the second phalanx of the index and middle finger of the non-dominant hand, using isotonic electrode paste as contact medium (Synapse, Kustomer Kinetics, Arcadia, CA, USA) and Brain Vision hard- and software for data acquisition (Brain Vision ExG Amplifier and Brain Vision Recorder; Brain Products, Munich, Germany). Data were recorded with an initial sampling rate of 1000 Hz (downsampled to 10 Hz), applying a low cut-off filter of 10 sec and a high cut-off filter of 250 Hz. A Matlab based application (Ledalab Version 3.3.4, Benedek and Kaernbach, 2010) was employed to run a discrete decomposition analysis from which through-to-peak values were used to calculate the sum amplitude of the first interval response (FIR) within a time window of 1–5 s after stimulus offset (response criterion 0.02 μS). SC data were range-corrected according to Lykken (1972). A three-factorial repeated ANOVA employing the factors "group", "CS" and "phase" (H1 H2, A1, A2, ET1, ET2, ET3, ER1, ER2, ER3) was employed. Due to technical failure, SC datasets from one patient and one HC were missing for day 3. $P < 0.05$ indicated statistical significance. If sphericity assumptions were not met, Greenhouse-Geisser corrections were applied.

3. Results

3.1. Sample characteristics and behavioral data

Sample characteristics are given in Table 1. Behavioral data for the fear conditioning task (ratings, SCR, contingency awareness) can be found in the supplement (supplemental data & figures S1, S2, S3). Briefly, we observed a main effect of conditioning in arousal ratings in the entire group, but no differences between patients and controls.

3.2. fMRI results

3.2.1. Differential conditioning and extinction effects in the combined sample

fMRI results for the main task effects are given in Table 2. During acquisition we observed, among others, activation in the right supplementary motor area (SMA), bilateral precentral gyri, and thalamus, in response to the CS+ > CS−. The extinction training activated the right thalamus, bilateral superior frontal gyri (SFG), bilateral insular cortices as well as the left inferior frontal operculum (IFO) and right SMA (Fig. 2). These activation patterns were mainly driven by the ET1 phase indicating the recall of the CR. During the early extinction recall on day 3 (ER1), the right angular gyrus and precuneus, left supramarginal gyrus and inferior parietal lobule showed heightened activation towards the CS+.

3.2.2. Group differences in differential conditioning, extinction training and recall

During early acquisition, patients exhibited stronger neural activation in the left fusiform gyrus, the right amygdala and the left insula in response to CS+ > CS− than HC. In turn, HC showed, among others, stronger activation of the right middle frontal gyrus (MFG) towards the CS+. On day 2, HC also showed, among others, enhanced activation in the left medial temporal gyrus (MTG), left medial SFG and in the left midcingulate and SMA (ET1). During early extinction recall on day 3, HC activated the right MFG stronger than patients. On the contrary, patients showed attenuated extinction recall during ER2 and 3 as indicated by stronger activation in the right insula (ER2), left IFO and the left inferior frontal gyrus (IFG) (ER3) (Fig. 3; Table 3).

4. Discussion

The present study employed a differential fear conditioning and delayed extinction paradigm on three consecutive days in patients with PD for the purpose of disentangling neural networks involved in fear acquisition, extinction and recall of fear-related memories to gain more insight into altered patterns of brain activation as a function of PD. Focusing on extinction recall may improve our understanding of how fear-inhibitory learning induced by behavioral exposure may be consolidated and retrieved in patients (Marin et al., 2014).

Two major effects were observed: first, on a neural level, PD patients were characterized by enhanced activation in networks subserving fear conditioning such as the amygdala or insula particularly during the initial trials of the acquisition phase, possibly indicating accelerated fear conditioning processes as a function of pathophysiology. Second, patients showed attenuated recall of extinction memories as indicated by sustained activation of fear circuitry networks encompassing the insula, IFO and IFG.

Table 1 Demographic and clinical sample characteristics.

	Patients ($n = 10$)	Controls ($n = 10$)	χ^2 or t (df)	p
Demographic characteristics				
Age	27.5 (8.5)	27.6 (8.0)	0.027 (18)	0.979
Female gender, *n* (%)	7 (70)	7 (70)	0.00 (1)	1.00
Right-handed, n (%)[a]	10 (100)	10 (100)	0.00 (1)	1.00
Smoker, *n* (%)[b]	3 (30)	2 (20)	0.148 (1)	0.701
Education, *n* (%)				
10 years	3 (30)	2 (20)	0.267 (1)	0.606
12–13 years	7 (70)	8 (80)		
Clinical characteristics				
CGI	4.3 (0.63)	-	-	-
PAS	20.0 (6.73)	-	-	-
SIGH-A	15.6 (6.75)	2.2 (2.39)	−5.91 (11.23)	<0.001
ASI	35.4 (10.1)	8.7 (5.12)	−7.44 (18)	<0.001
BDI-II	10.9 (5.36)	1.1 (1.85)	−5.46 (11.12)	<0.001

CGI: Clinical Global Impression; PAS: Panic and Agoraphobia Scale; SIGH-A: Structured Interview Guide for the Hamilton Anxiety Scale; ASI: Anxiety Sensitivity Index; BDI-II: Beck Depression Inventory II

[a] available for $n = 19$

[b] available for $n = 19$

Values given as mean (standard deviation) except where noted.

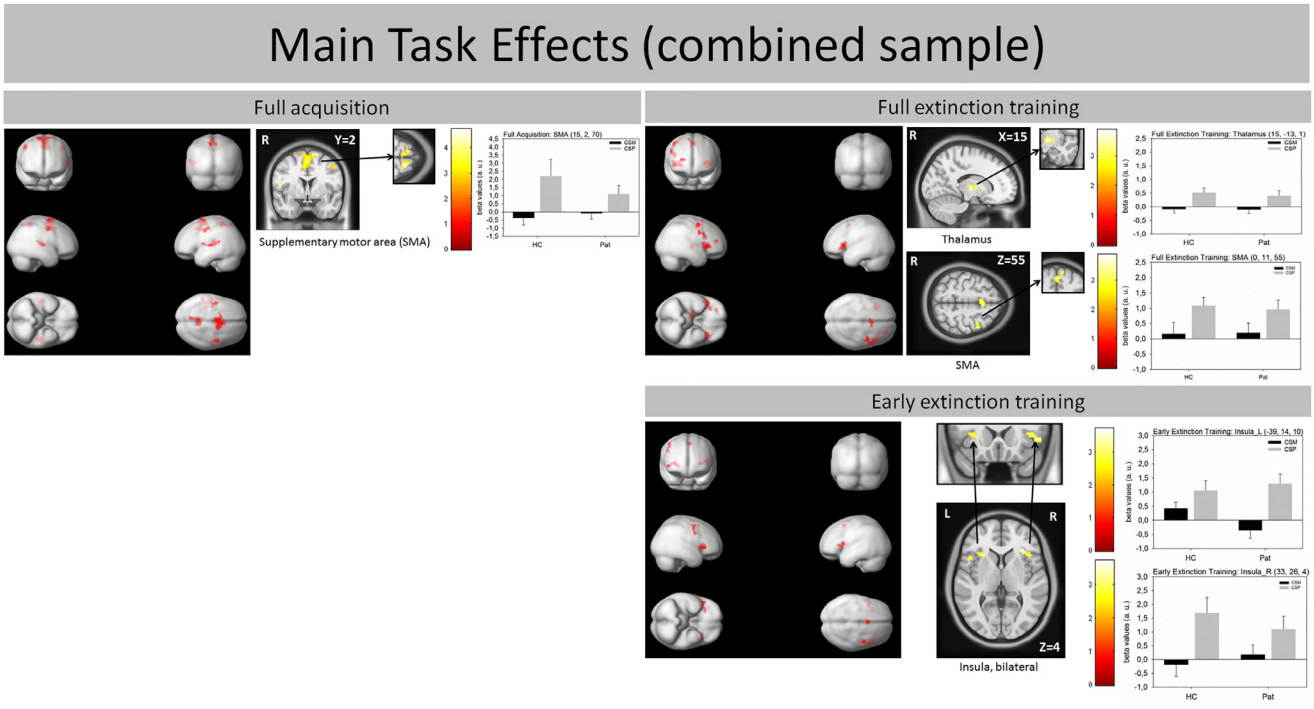

Fig. 2 Neural markers of differential fear conditioning for the combined sample for the contrast CS+ > CS−. CS+: conditioned stimulus (CS) followed by the unconditioned stimulus (US); CS−: CS never followed by the US. Left: full acquisition. Right: full and early extinction training.

4.1. Neural networks of fear conditioning, extinction training and recall

In line with expectations, stronger neural activation during day 1 in networks conferring differential fear conditioning such as the SMA, superior temporal gyrus or thalamus (Fullana et al., 2016; Sehlmeyer et al., 2009) were observed in the entire group, indicating that successful conditioning was induced. Due to power restrictions in this small sample, no effects on autonomic responding were observed, but higher arousal ratings for the CS+ after the fear acquisition phase also supported the conditioning effects. Interestingly, neural activation patterns during day 2 could be mainly traced back to the early extinction phase, which

Table 2 Brain activation patterns during fear acquisition, extinction and extinction recall to conditioned stimulus (CS+ vs. CS−) for the combined sample.

Contrast/Region	Side	Voxels	x	y	z	t	p
Combined sample							
Full acquisition: ACS+ > ACS−							
Supplementary motor area	R	309	15	2	70	4.73	<0.001
Rolandic operculum	L	123	−33	−28	16	4.28	<0.001
Heschl gyrus	R	62	48	−19	7	4.06	<0.001
Precentral gyrus	L	41	−45	−4	40	3.63	<0.001
Precuneus	R	110	−6	−46	52	3.41	<0.001
Precentral gyrus	R	40	45	−1	46	3.35	<0.001
Early acquisition: A1CS+ > A1CS−							
Supplementary motor area	L	100	−9	5	49	3.77	<0.001
Precentral gyrus	R	16	48	−4	49	3.11	0.001
Late acquisition: A2CS+ > A2CS−							
Parahippocampal gyrus	R	24	6	−13	−20	4.07	<0.001
Supplementary motor area	R	124	12	−1	73	4.01	<0.001
Superior temporal gyrus	R	132	−45	−34	10	3.97	<0.001
Heschl gyrus	R	74	39	−31	16	3.66	<0.001
Precuneus	R	61	6	−52	52	3.54	<0.001
Pallidum	L	44	−12	2	−2	3.38	<0.001
Thalamus	R	25	9	−22	1	3.36	<0.001
Putamen	R	17	18	11	1	3.13	0.001
Full extinction training: ETCS+ > ETCS−							
Thalamus	R	62	15	−13	1	3.88	<0.001
Superior frontal gyrus	R	25	27	44	13	3.86	<0.001
Inferior frontal gyrus	L	85	−36	20	7	3.72	<0.001
Insula	R	109	45	20	1	3.57	<0.001
Middle frontal gyrus	R	24	45	2	55	3.29	0.001
Supplementary motor area	R	39	0	11	55	3.21	0.001
Precentral gyrus	R	39	51	2	34	3.15	0.001
Early extinction training: ET1CS+ > ET1CS−							
Insula	R	73	33	26	4	3.72	<0.001
Inferior frontal operculum	L	31	−42	14	10	3.63	<0.001
Supplementary motor area	L	28	0	11	55	3.62	<0.001
Insula	L	17	−27	20	4	3.06	0.001
Precentral gyrus	R	27	51	2	37	3.00	0.001
Mid extinction training: ET2CS+ > ET2CS−					No differential activation		
Late extinction training: ET3CS+ > ET3CS−							
Superior frontal gyrus	R	46	30	59	13	3.59	<0.001
Thalamus	L	30	−3	−22	−5	3.32	0.001
Full extinction recall: ERCS+ > ERCS−					No differential activation		
Early extinction recall: ER1CS+ > ER1CS−							
Angular gyrus	R	46	30	−46	40	3.73	<0.001
Supramarginal gyrus	L	32	−54	−28	34	3.52	<0.001
Precuneus	R	23	21	−70	43	3.37	<0.001
Inferior parietal lobule	L	28	−48	37	46	3.00	0.001
Mid extinction recall: ER2CS+ > ER2CS−					No differential activation		
Late extinction recall: ER3CS+ > ER3CS−					No differential activation		

CS: conditioned stimulus; CS+: CS that is followed by an unconditioned stimulus; CS−: CS that is never followed by the US; *L*: left; *R*: right; voxel: number of voxels per cluster; *x, y, z*: MNI coordinates. Whole-brain results at $p < 0.005$ (uncorr.) with a minimum cluster size of 15 contiguous voxels.

we thought to capture the recall of the overnight consolidated fear conditioning memory trace. Supporting this assumption, we predominantly observed activation in fear circuitry networks such as the bilateral insula, left IFO and bilateral SMA. The present experimental design explicitly allowed for consolidation of fear conditioning and extinction memories. We conclude that at least the initial trials of fear extinction tasks rather indicate recalling fear memories, than reflecting fear-inhibitory processes yet. These findings emphasize methodological limitations of combined one-session fear conditioning and extinction tasks as previously conducted by the majority of studies in this field.

We were not able to identify clear-cut neural substrates of extinction training in contrast to other neuroimaging

Table 3 Brain activation patterns during fear acquisition, extinction and extinction recall to conditioned stimulus (CS+ vs. CS−) for patients vs. healthy controls and vice versa.

Contrast/Region	Side	Voxels	x	y	z	t	p
PAT > HC							
Full acquisition: ACS+ > ACS−							
Hippocampus	R	16	33	−4	−17	3.63	<0.001
Superior temporal gyrus	R	19	45	−4	−11	2.90	0.002
Early acquisition: A1CS+ > A1CS−							
Fusiform gyrus	L	178	−36	−25	−20	3.82	<0.001
Amygdala[1]	R	91	33	−4	−14	3.48	<0.001
Insula	L	16	−30	−13	19	3.30	<0.001
Vermis 4 5		19	−3	−55	−26	3.20	0.001
Cerebellum 6	L	37	−12	−64	−14	3.20	0.001
Late acquisition: A2CS+ > A2CS−					No differential activation		
Full extinction training: ETCS+ > ETCS−					No differential activation		
Early extinction training: ET1CS+ > ET1CS−					No differential activation		
Mid extinction training: ET2CS+ > ET2CS−					No differential activation		
Late extinction training: ET3CS+ > ET3CS−					No differential activation		
Full extinction recall: ERCS+ > ERCS−					No differential activation		
Early extinction recall: ER1CS+ > ER1CS−					No differential activation		
Mid extinction recall: ER2CS+ > ER2CS−							
Insula	R	29	42	5	−5	3.56	<0.001
Late extinction recall: ER3CS+ > ER3CS−							
Inferior frontal operculum	L	19	−42	14	19	3.20	0.001
Inferior frontal gyrus	L	16	−30	41	−2	2.88	0.002
HC > PAT							
Full acquisition: ACS+ > ACS−					No differential activation		
Early acquisition: A1CS+ > A1CS−							
Middle frontal gyrus	R	39	24	29	37	3. 13	0.001
Late acquisition: A2CS+ > A2CS−							
Rolandic operculum	R	233	42	−25	22	4.17	<0.001
Postcentral gyrus	L	146	−42	−19	43	3.82	<0.001
Postcentral gyrus	L	36	−60	−19	22	3.62	<0.001
Postcentral gyrus	L	17	−54	−4	13	3.54	<0.001
Inferior parietal lobule	L	22	−57	−37	46	3.28	0.001
Precentral gyrus	R	21	39	−4	40	3.14	0.001
Full extinction training: ETCS+ > ETCS−							
Middle temporal gyrus	L	35	−54	−34	−14	3.24	0.001
Medial superior frontal gyrus	L	21	−3	29	61	3.19	0.001
Precuneus	L	19	−6	−52	34	3.05	0.001
Early extinction training: ET1CS+ > ET1CS−							
Midcingulate cortex	L	37	−15	2	34	3.94	<0.001
Supplementary motor area	L	38	0	20	64	3.24	0.001
Precuneus	R	18	6	−73	43	3.11	0.001
Supramarginal gyrus	R	20	45	−43	25	2.99	0.001
Mid extinction training: ET2CS+ > ET2CS−					No differential activation		
Late extinction training: ET3CS+ > ET3CS−					No differential activation		
Full extinction recall: ERCS+ > ERCS−					No differential activation		
Early extinction recall: ER1CS+ > ER1CS−							
Supramarginal gyrus	R	15	54	−43	31	3.38	<0.001
Middle frontal gyrus	R	15	39	11	37	3.26	0.001
Mid extinction recall: ER2CS+ > ER2CS−					No differential activation		
Late extinction recall: ER3CS+ > ER3CS−					No differential activation		

CS: conditioned stimulus; CS+: CS that is followed by an unconditioned stimulus; CS−: CS that is never followed by the US; *L*: left; *R*: right; voxel: number of voxels per cluster; *x, y, z*: MNI coordinates.

Whole-brain results at $p < 0.005$ (uncorr.) with a minimum cluster size of 15 contiguous voxels.

[1] cluster encompassing Hippocampus and Insula.

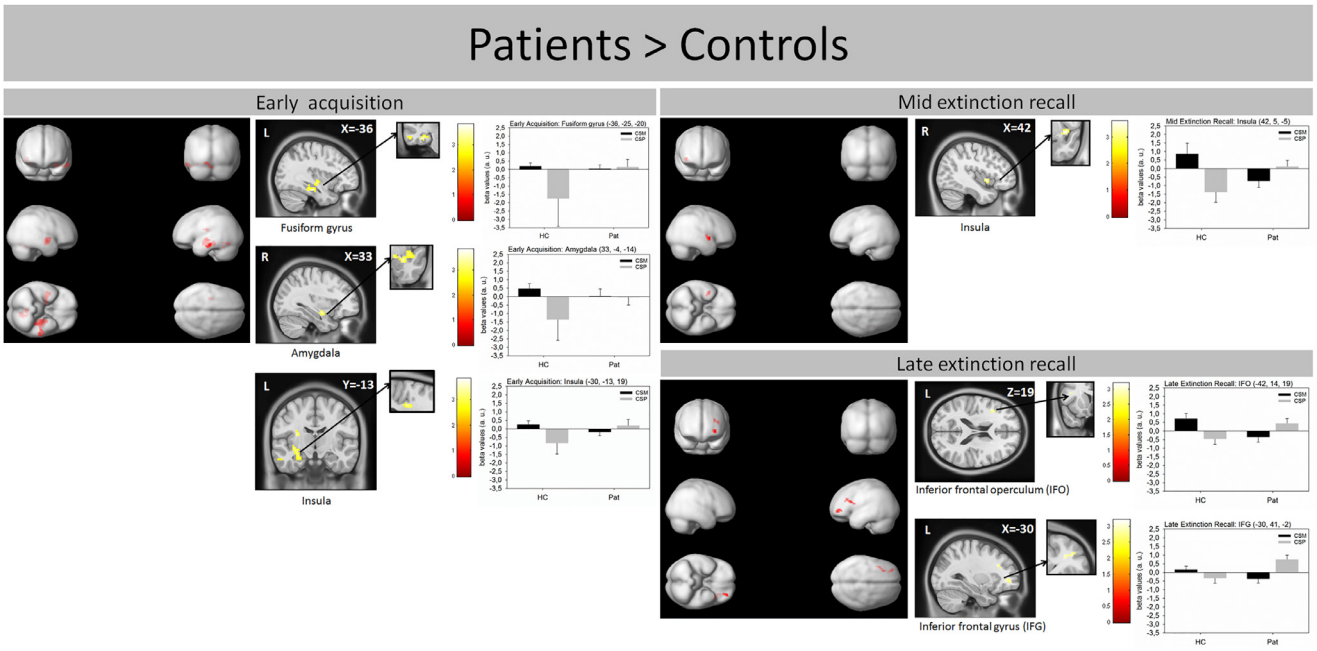

Fig. 3 Neural markers of differential fear conditioning for patients vs. healthy controls: CS+: conditioned stimulus (CS) followed by the unconditioned stimulus (US); CS−: CS never followed by the US. Left: full acquisition. Right: full and early extinction training.

studies who suggest an extinction network including the amygdala, anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), insula and (vm)PFC (Sehlmeyer et al., 2009). Again, power limitations due to the sample size may account for these null-findings: effects of fear conditioning are usually well pronounced and thus detectable in smaller samples, however, this may not refer to extinction processes. Alternatively, the timely dynamics of extinction may vary between subjects, making it difficult to trace them on a group level, although we took temporal dynamics into account using an early and late extinction training phase. Instead, the SFG, which is associated with cognitive control and response inhibition (Boisgueheneuc et al., 2006; Floden and Stuss, 2006) activated stronger during the late extinction training. This finding could imply that increased cognitive control may be gained during extinction training, possibly reflecting alternative (e.g., cognitively mediated) routes of fear inhibition.

For extinction recall during day 3, we found stronger activation in the angular gyrus and the neighboring supramarginal gyrus as well as the right precuneus. These brain areas are involved in memory retrieval and general attention (Lundstrom et al., 2005; Seghier, 2013) and enhanced activation may reflect attentional shifts towards the more salient CS+. However, no neural substrates as derived from animal studies encompassing the (ventro-)medial PFC (Milad and Quirk, 2002) could be identified as a function of extinction recall. Although increased, yet unspecific attentional network activation was observed during the initial trials of day 3, no return of fear seemed to take place. We assume this null-finding to be a consequence of the relatively higher number of trials used for extinction training during day 2, possibly resulting in a very robust fear inhibition. As results for PD patients do however show, this learning and retrieval gradient may differ as a function of pathophysiology, as reflected by floor effects in controls, but not in patients.

In summary, present findings support the notion of successful conditioning induced by the novel paradigm. Moreover, we were able to disentangle conditioning and extinction processes and show that neural substrates during extinction training (day 2) most likely reflect the recall of conditioned responses. Future studies should focus more strongly on targeting the neural substrates of extinction recall in human samples, which are still not fully understood.

4.2. Altered neural networks of fear conditioning, extinction training and recall in PD patients

On day 1 we observed differential activation during the first trials of the acquisition in patients vs. HC. While HC initially showed a pronounced deactivation in fear circuitry regions towards the CS+, patients exhibited stronger activation in the left fusiform gyrus, right amygdala and left insula. We assume that this deactivation in HC might represent a latent inhibition phenomenon (the effect that familiar stimuli take longer to become a CS than new stimuli; Lubow, 1973) due to the relatively prolonged habituation phase. Likewise, stronger MFG deactivation in patients towards CS+ may reflect a lack of this top-down inhibition. Differences in neural activation patterns during fear conditioning were predominantly observed in fear circuitry networks: the fusiform gyrus, including the fusiform face area (FFA) is known to play a role in face recognition (Weiner and Zilles, 2016). As both CSs were faces, early recognition of perceptual features from salient stimuli such as the CS+ appeared to be amplified during fear

conditioning in PD patients. In line, the amygdala and insula, as key regions conferring fear conditioning (LeDoux, 2000; Sehlmeyer et al., 2009) were recruited in patients to a greater extent. We conclude that these findings may serve as initial evidence for accelerated fear conditioning processes in PD possibly representing either a vulnerability for the development, or a consequence of the disorder. As a vulnerability factor, accelerated emotional-associative learning may lead to a greater sensitivity towards aversive events mediated by a faster and stronger linking of former neutral and aversive cues - making people more prone to develop anxiety disorders like PD. Of note, patients showed no differential activation during extinction training on day 2 unlike we expected. However, HC showed even stronger activation in the left MTG, associated with multimodal semantic processing (Visser et al., 2012), and the left medial SFG, associated with cognitive control and attention set shift between object features (Nagahama et al., 1999). This could represent a stronger sensory processing of the CS+ in HC.

During extinction recall on day 3, we observed stronger neural responding in the right insula, the left IFO and the left IFG in patients. These findings point towards deficits in extinction recall rather than training. In contrast, HC showed stronger activation of the right MFG towards the CS+ already during early ER which might reflect a more efficient recall of extinction memory and hence, stronger top-down suppression of CS+ responding (similar to effects during early acquisition). Heightened insular activation during mid extinction recall in patients, on the other hand, is interpreted as attenuated fear inhibition with stronger activation of defensive networks. The left IFG is known to be involved in response inhibition and inhibitory processes in general (Swick et al., 2008). Findings may indicate stronger suppression of behavioral tendencies in response towards the (still) fear eliciting CS+ in patients even during the recall of extinction memories. Results support previous findings on the association of increased IFG activation as a feature of fear conditioning in PD (Kircher et al., 2013; Lueken et al., 2014) that was modulated by CBT (Kircher et al., 2013) which is based on the principles of extinction. Laboratory studies show that even if fears are easy to extinguish, they recover yet more easily, i.e. extinction may be easy to learn but hard to remember (Vervliet et al., 2013). This raises the question if there is maybe not (only) a deficit in extinction training in PD but -in the long run even more debilitating - in extinction recall, like it has been found to be the case in other anxiety disorders like obsessive-compulsive disorder (OCD; Milad et al., 2013) and posttraumatic stress disorder (PTSD; Rougemont-Bücking et al., 2011). PTSD can be characterized by pathological fear memories - either in the acquisition of fear memories or as pathologies in the expression of an otherwise normal fear memory (VanElzakker et al., 2014). This has important implications for the treatment as exposure therapy is thought to instantiate fear-inhibitory memories for long-term recall with a focus on relapse prevention (Vervliet et al., 2013).

Neurostimulatory and neuromodulatory treatments bear potential as neuroscience-informed treatment strategies since they may provide access to basic emotional-associative learning processes and memory circuitries (Ressler and Mayberg, 2007) and could be useful tools for augmenting fear extinction. In the long run it would be ideal to use these promising methods combined with exposure therapy to promote the formation of a strong memory trace during extinction which would reduce the risk of relapse (Marin et al., 2014). Future studies are however needed as a proof of this hypothesis.

4.3. Limitations

Due to the demanding paradigm requiring three consecutive days, the sample with complete data was rather small, pointing towards limitations in conducting sophisticated experimental designs particularly in vulnerable patient groups. Future studies are nevertheless encouraged to replicate these preliminary results. Employing a habituation phase can furthermore significantly reduce conditioning-related activations of several characteristic brain regions (Fullana et al., 2016). As such, the finding of accelerated conditionability in patients has to be interpreted within the phenomenon of latent inhibition, which may be attenuated in patients. Context conditioning within the scanner may have occurred as a neuroimaging environment represents a unique context that cannot be changed during an experimental session (VanElzakker et al., 2014). The MRI-scanner itself can represent a threatening situation for anxiety patients, and those suffering from PD and agoraphobia may be especially sensitive to the stress-eliciting properties of the scanner. However, habituation to the scanner environment is frequently seen in patients and controls (Lueken et al., 2011) and subjective ratings after habituation between patients and controls speak in favor of comparable arousal levels. Nevertheless, an anxious control group would have been of particular value to investigate the transdiagnostic nature of our findings.

4.4. Conclusions and future directions

The present study supports the notion of aberrant neurofunctional activation patterns during emotional-associative learning in PD patients with particular focus on the rapid acquisition of fear memories and impaired recall of extinction memories. Since laboratory fear extinction learning and recall bears similarities to exposure therapy and clinical relapse, it is of pivotal interest to better understand the underlying mechanisms in order to inform novel treatment approaches. Nevertheless, taking into account the interoceptive nature of PD, further studies using interoceptive conditioning paradigms are needed to shed additional light on the commonalities and differences between interoceptive and exteroceptive emotional-associative learning in PD patients. Future studies should investigate the predictive value of experimental measures of extinction recall for clinical relapse and its implications for exposure-based therapy since failing to recall extinction memories increases the risk for the return of fear and consequently for relapse. Predicting which patient may be vulnerable for relapse could help in supporting clinical decision making on individually tailored treatment approaches. A better understanding of those mechanisms subserving memory consolidation and recall of fear-inhibitory memories could improve measures against clinical relapse.

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Contributors

Author Schwarzmeier has contributed to the data analysis, literature searches, and manuscript preparation. Author Kleint has contributed to the data collection and approved the final manuscript. Authors Wittchen, Ströhle and Hamm have contributed to the study design and approved the final manuscript. Author Lueken has contributed to the study design, data analysis, literature searches, manuscript preparation and approved the final manuscript.

Conflict of interest

The following authors report no conflicts of interest concerning the content of this paper: H. Schwarzmeier, N. I. Kleint, A. Hamm, U. Lueken. H.-U. Wittchen has been member of advisory boards of several pharmaceutical companies. He received travel reimbursements and research grant support from Essex Pharma, Sanofi, Pfizer, Organon, Servier, Novartis, Lundbeck, Glaxo Smith Kline. A. Ströhle received research funding from the German Federal Ministry of Education and Research, the European Commission (FP6) and Lundbeck, and speaker honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co, Lundbeck, Pfizer, Wyeth and UCB. Educational grants were given by the Stifterverband für die Deutsche Wissenschaft, the Berlin Brandenburgische Akademie der Wissenschaften, the Boehringer Ingelheim Fonds and the Eli Lilly International Foundation.

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Supplementary materials

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